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(54) Title: CHELATING AGENTS

(57) Abstract

Chelants of formula (I) (as given in claim 1) are disclosed. The chelants are of particular use in producing therapeutic, diagnostic and detoxification agents.

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CHELATING AGENTS

The present invention relates to chelating agents, more particularly aminopolycarboxylic acid chelants, and metal chelates thereof and the use of such chelating agents and chelates in diagnostic imaging, radiotherapy or heavy metal detoxification.

Medical uses of chelating agents are well established, for example as stabilizers for pharmaceutical preparations, as antidotes for poisonous heavy metal species and as agents for the administration, in chelate form, of metal ions for radiotherapy or diagnostic imaging, e.g. X-ray, magnetic resonance imaging (MRI), ultrasound or scintigraphy.

Aminopolycarboxylic acids and derivatives thereof (hereinafter referred to as APCAs) are well known as particularly effective chelants and are described in a wide range of publications, for example in US-A-2407645 (Bersworth), EP-A-71564 (Schering), EP-A-130934 (Schering), EP-A-165728 (Nycomed), US-A-4647447 (Schering), US-A-4826673 (Mallinckrodt), US-A-4639365 (Sherry) and EP-A-299795 (Nycomed) and in the documents cited in these patent publications.

Thus, for example, EP-A-71564 describes paramagnetic metal chelates, for which the chelating agent is nitrilotriacetic acid (NTA), N,N,N',N'-ethylenediamine-tetraacetic acid (EDTA), N-hydroxyethyl-N,N',N'-ethylenediamine-triacetic acid (HEDTA), N,N,N',N",N"-diethylenetriamine-pentaacetic acid (DTPA) and N-hydroxyethylimino-diacetic acid, as being suitable as contrast agents for MRI, contrast being achieved by the effect of the magnetic field of the paramagnetic species (e.g. Gd(III)) with the chelating agents serving to reduce the toxicity and to assist administration of the paramagnetic species. Amongst the particular metal chelates disclosed by

EP-A-71564 was the dimeglumine salt of Gd DTPA, the use of which as an MRI contrast agent has recently received much attention. The Gd(III) chelate of 1,4,7,10-tetraazacyclododecanetetraacetic acid (DOTA), referred to in DE-A-3401052 (Schering) and in US-A-4639365 (University of Texas), has also recently received attention in this regard.

To improve stability, water solubility and selectivity, relative to the APCA chelating agents described in EP-A-71564, Schering in EP-A-130934, have proposed the partial substitution for the N-attached carboxyalkyl groups of alkyl, alkoxyalkyl, alkoxy carbonylalkyl or alkylaminocarbonylalkyl groups, where any amide nitrogens may themselves carry polyhydroxy-alkyl groups.

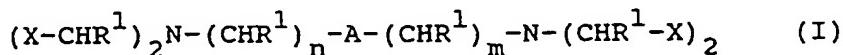
For reduced toxicity, Salutar Inc, in for example US-A-4687659, has proposed the use as MRI contrast agents of chelates of paramagnetic metal ions and bisamides of DTPA, in particular DTPA-bismethylamide.

In EP-A-299795, Nycomed proposed several further novel APCA chelants of linear, branched and cyclic structures which optionally carried hydrophilic groups in the carbon chains linking the amine nitrogens.

There is however a general and continuing need for APCA chelants which form metal chelates of reduced toxicity, improved stability, improved water solubility or improved biodistribution (e.g. enhanced tissue or organ specificity).

We now propose certain improved chelating agents, in particular tertiary amide derivatives of APCAs.

Viewed from one aspect therefore the invention provides chelants of formula I



(wherein

A represents a group $>NCHR^1X$ or $>N(CHR^1)_pN(CHR^1X)_2$ or

$A(CHR^1)_m$ represents a carbon nitrogen bond; each X which may be the same or different represents a carboxyl group or a derivative thereof or a group R^1 ; each R^1 which may be the same or different represents a hydrogen atom, a mono- or poly-hydroxyalkyl group or an alkoxy or alkoxyalkyl group optionally mono or polysubstituted by hydroxy and/or alkoxy groups; and n, m and p are each 2,3 or 4, preferably 2; with the provisos that in at least two CHR^1X moieties X is a carboxyl group or a derivative thereof, that at least one group X, and preferably at least 2, is of formula $CONR^2_2$ where each R^2 , which may be the same or different, represents an alkyl group optionally mono- or polysubstituted by hydroxy and/or alkoxy groups or NR^2_2 represents a nitrogen-attached 5 to 7 membered saturated heterocyclic ring optionally containing a nitrogen, oxygen or sulphur atom as a further ring heteroatom and optionally substituted by one or more hydroxyl and/or R^1 groups and that at least one R^1 in a moiety (CHR^1X) , $(CHR^1)_m$, $(CHR^1)_n$ or $(CHR^1)_p$ is other than hydrogen) and metal chelates and salts thereof.

Preferably each group CHR^1X in the compounds of formula I is other than a methyl group.

Particularly preferably, where no NR^2_2 moiety is a heterocyclic ring and where no R^1 group in a CHR^1X is a hydrophilic group or (more especially) no R^1 group in a $(CHR^1)_m$, $(CHR^1)_n$ or $(CHR^1)_p$ moiety is a hydrophilic group, then at least one group X is of formula $CONR^2_2$ where each R^2 is an optionally mono- or polyhydroxylated alkyl group or a mono or polyhydroxylated alkoxy- or polyalkoxy- alkyl group, particularly preferably a group hydroxy substituted at at least the terminal (omega) carbon.

Unless specified otherwise, all alkyl or alkylene moieties in the compounds of the invention preferably contain up to 8, particularly preferably up to 6, carbon atoms. Thus in the compounds of formula I, each hydrophilic R^1 group, which may be straight-chained or

branched, preferably has a carbon atom content of from 1 to 8, especially preferably 1 to 6 carbon atoms. The R¹ groups may be alkoxy, polyalkoxy, hydroxyalkoxy, hydroxypolyalkoxy, polyhydroxyalkoxy, alkoxyalkyl, polyhydroxyalkyl, hydroxyalkoxyalkyl, hydroxypoly-alkoxyalkyl or polyhydroxypolyalkoxyalkyl groups, but more preferably they will be monohydroxyalkyl or polyhydroxyalkyl groups. The hydrophilic R¹ groups serve to increase the hydrophilicity and reduce the lipophilicity of the metal chelates formed with the chelating agents of the invention and it is preferred that the compounds of formula I should contain from 1 to 4 hydrophilic R¹ groups.

As hydrophilic R¹ groups, the compounds of the invention may thus include for example hydroxymethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 3-hydroxypropyl, 2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl, 1-(hydroxymethyl)-2-hydroxyethyl, methoxymethyl, ethoxymethyl, 2-hydroxyethoxymethyl, methoxyethoxymethyl, (2-hydroxyethoxy)ethyl, etc groups.

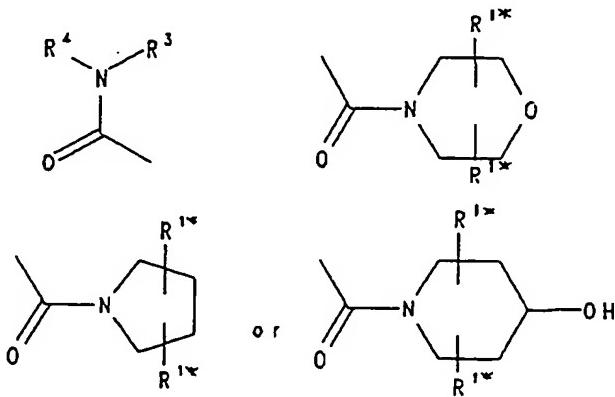
The carboxyl derivatives which may be represented by the groups X in the compounds of formula I may include for example, amide groups, ester groups and carboxylate salt groups, for example groups of formulae CONR¹¹₂ (where R¹¹ is a hydrogen atom or a group R² or NR¹¹₂ is a heterocyclic group as defined for NR²₂ above), COOR¹² (where R¹² is a hydrogen atom or an optionally hydroxylated, optionally alkoxylated alkyl group) and -COOM (wherein M⁺ is a monovalent cation or a fraction of a polyvalent cation, for example an ammonium or substituted ammonium ion or a metal ion, for example an alkali metal or alkaline earth metal ion). Particularly preferably, M⁺ is a cation deriving from an organic base, for example meglumine.

It is also particularly preferred that the number of the ion-forming X groups in the compounds of formula I be chosen to equal the valency of the metal species to

be chelated by the compound of formula I. Thus, for example, where Gd(III) is to be chelated, the chelating agent of formula I preferably contains three ion-forming X groups, for example -COOH or -COOM. In this way, the metal chelate will be formed as a neutral species, a form preferred since the osmotic pressures in concentrated solutions of such compounds are low and since their toxicities relative to their ionic analogues are significantly reduced.

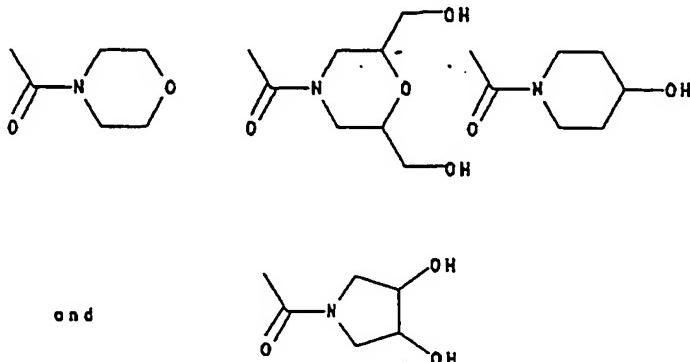
Compounds of formula I in which all the carboxyl or carboxyl derivative X groups are -COOH, -COOM or CONR¹¹₂ groups are especially preferred since compositions containing such metal chelates can readily be sterilized, for example by autoclaving. Moreover compounds in which each group CH₂R¹X is of formula CH₂X' (where X' is a carboxyl group or a derivative thereof are particularly preferred.

In the chelants of the invention, it is especially preferred that at least one X group is of formula



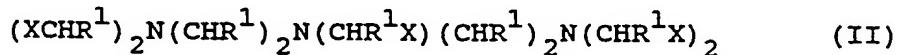
(where R¹¹ is an hydroxyl group or an R¹ group as hereinbefore defined, R³ is an alkyl group, particularly a C₁₋₃ alkyl group, and R⁴ is an alkyl, hydroxyalkyl or hydroxy-alkoxyalkyl group, particularly one in which the alkyl or alkylene moieties contain 1 to 3 carbons). Particularly preferred examples include

$-\text{CON}(\text{CH}_3)\text{CH}_2\text{CHOHCH}_2\text{OH}$, $-\text{CON}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$,
 $-\text{CON}(\text{CH}_3)_2$, $-\text{CON}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OCH}_2\text{CHOHCH}_2\text{OH}$,



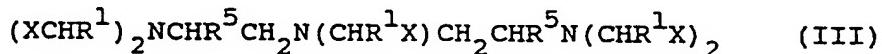
In the chelants of the invention, it is especially preferred that the terminal amine nitrogens each carry one group CHR^1X in which X represents a tertiary amide group CONR_2^2 .

Particularly preferred compounds according to the invention include the chelants of formula II



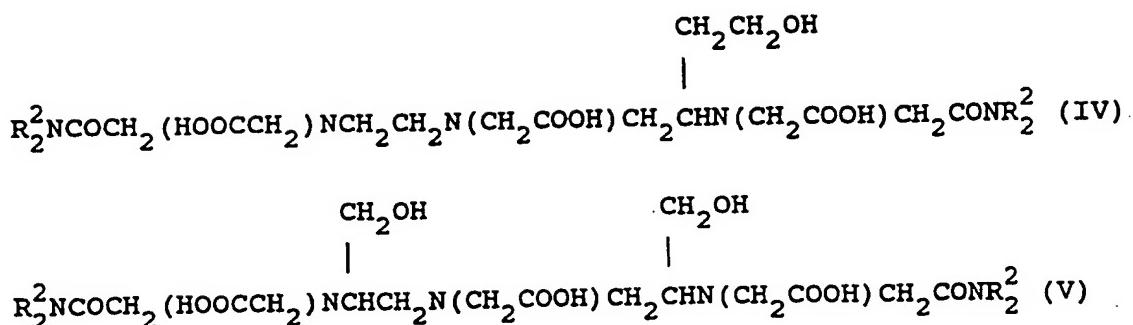
(where X and R¹ are as hereinbefore defined) and the metal chelates and salts thereof.

Chelants of formula III



(where one R⁵ group is a hydroxy(C₁₋₄)alkyl group and the other R⁵ group is a hydrogen atom or a hydroxy(C₁₋₄)alkyl group and X and R¹ are as hereinbefore defined) and the metal chelates and salts thereof are particularly preferred.

Chelants of formulae IV and V



(where NR_2^2 is as hereinbefore defined) and the metal chelates and salts thereof are also particularly preferred.

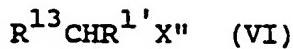
The chelant compounds of the invention may be prepared in the manner described by Nycomed in EP-A-299795.

Thus viewed from a further aspect the invention provides a process for the preparation of compounds of formula I, said process comprising at least one of the following steps:

- i) reacting a corresponding amine to introduce a CHR^1X moiety at an amine nitrogen;
- ii) converting a carboxyl X moiety in a corresponding compound into a carboxyl derivative thereof or converting an carboxyl derivative X^1 moiety in a compound of formula I into a carboxyl group; and
- iii) converting a compound of formula I into a salt or metal chelate thereof or converting a salt or metal chelate of a compound of formula I into a compound of formula I.

Process step (i) may conveniently be performed by reacting a compound essentially of formula I but having at least one hydrogen atom or other readily displaceable group or moiety in place of a CHR^1X moiety and optionally having in place of X and/or R^1 moieties groups convertible thereto (for example groups convertible by the removal of protecting groups), with a

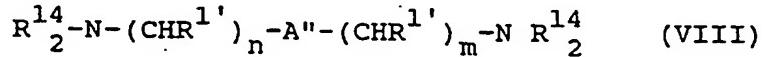
compound of formula VI



(wherein R^{13} is a leaving group, for example a nucleophilically displaceable group such as a halogen atom, preferably a bromine atom; and $R^{1'}$ and X'' , which are not both hydrogen atoms, are as defined for R^1 and X or are groups convertible thereto, for example by deprotection).

As protecting groups, conventional protecting groups may be used, for example groups such as are described by T.W. Greene in "Protective Groups in Organic Synthesis", John Wiley & Sons, 1981. For the protection of hydroxyl groups particular mention may be made however to the utility of benzyl protecting groups which are stable over a wide pH range but are readily removed by hydrogenolysis as described by T.W. Greene. Polyhydroxyalkyl groups may for example alternatively be protected in the form of cyclic polyether groups, for example as 2,2-dimethyl-1,3-dioxacyclopent-4-yl groups, as such cyclic polyether groups can be opened by acid hydrolysis to leave the unprotected polyhydroxyalkyl group.

Thus for example, introduction of a $-CHR^{1'}X$ moiety may be effected by reacting an amine of formula VIII



(wherein R^{14} is a hydrogen atom or a $CHR^{1'}X''$ group; X'' and $R^{1'}$ are as defined above; and A'' is a group NR_2^{14} or $N(CHR^{1'})_pNR_2^{14}$ or $A''(CHR^{1'})_m$ is a carbon nitrogen bond; with the provisos that at least one R^{14} is a hydrogen atom or a readily displaceable group or NR_2^{14} represents a cyclic group readily subject to ring-opening at the nitrogen, at least one $R^{1'}$ in $(CHR^{1'})_n$, $(CHR^{1'})_m$ or $(CHR^{1'})_p$ is other than hydrogen and that at least two

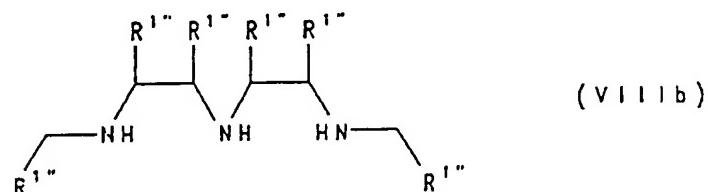
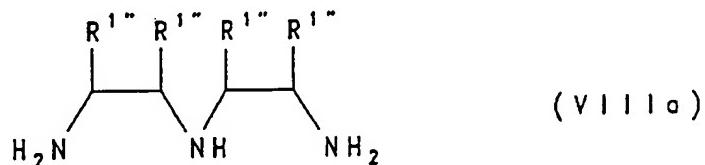
amine nitrogens carry a hydrogen atom or a -CHR¹X"

moiety in which X" is as defined above or is convertible to a carboxyl group or a derivative thereof) with a compound of formula VI (as defined above), followed if required by converting R¹ or X" to R¹ or X and/or by converting one or more X or X" groups to CONR₂².

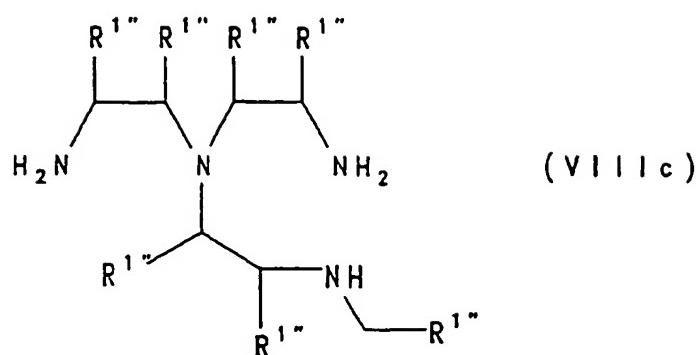
The process of step (i) is particularly preferably effected by reacting a compound of formula VI (in which any hydroxyl moieties are protected) with bromoacetic acid or a derivative thereof, for example the lithium salt or an ester, followed by deprotection of the hydroxyl moieties and amidation.

To introduce -CHR¹X groups wherein R¹ is hydroxy or hydroxyalkyl, alternative compounds of formula VI such as 3-bromooxacyclopentan-2-one, HalCH₂CH₂OH, HalCH₂CHOHCH₂OH or R⁶-O-CH₂-CHHal-COOH (wherein Hal is a halogen atom such as a bromine atom and R⁶ is a protecting group) may of course be used.

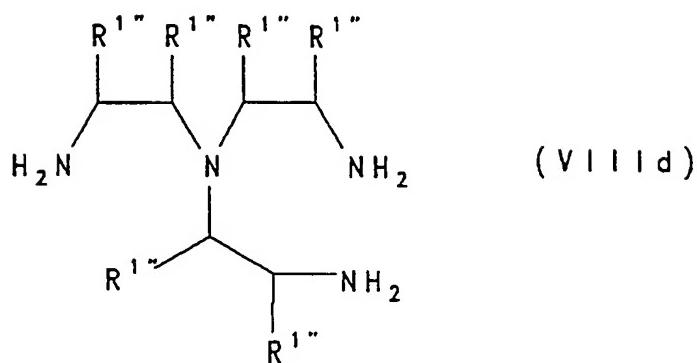
Thus for the process of step (i) the following preferred starting compounds of VIII may be used:



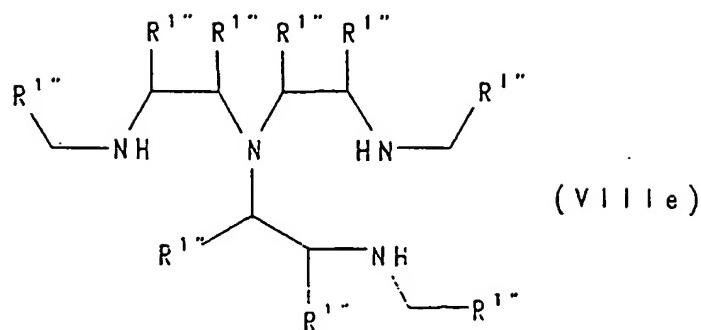
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(VIIIc)

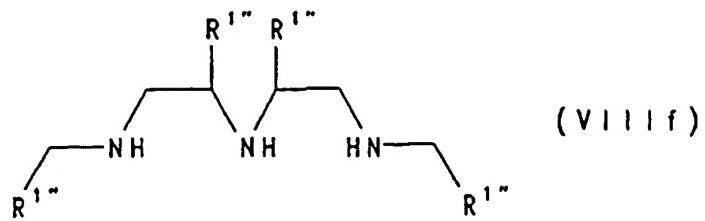


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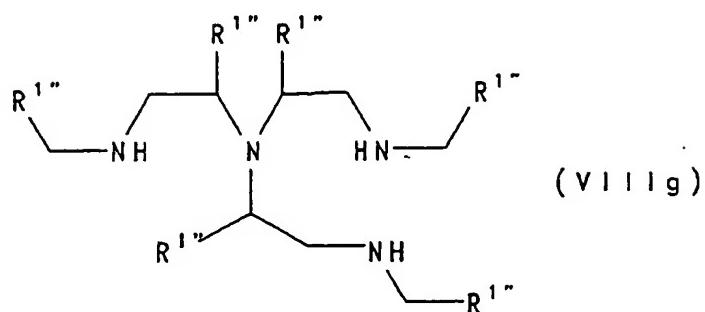


(VIIIf)

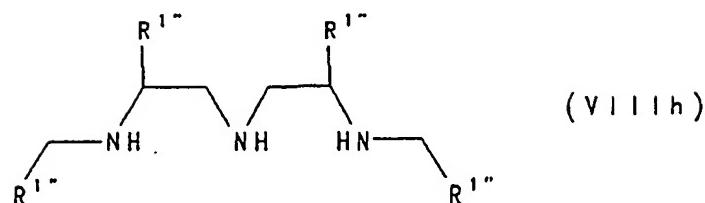
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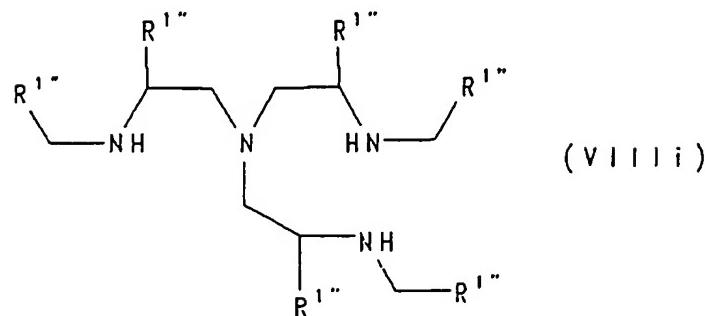
(VIII f)



(VIII g)

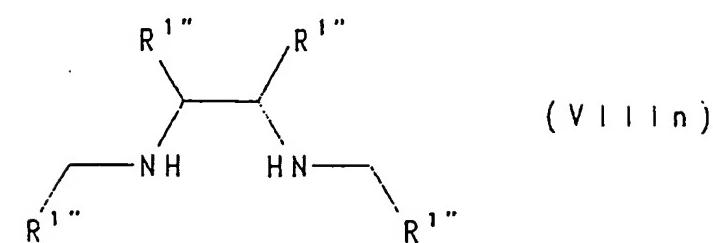
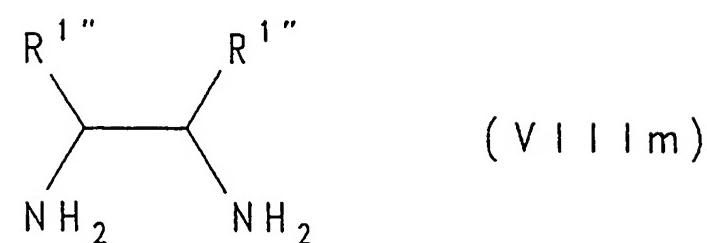
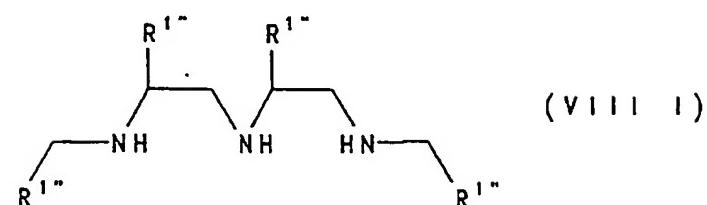
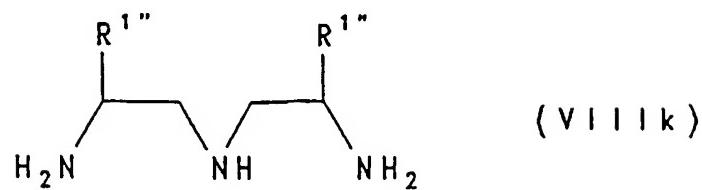
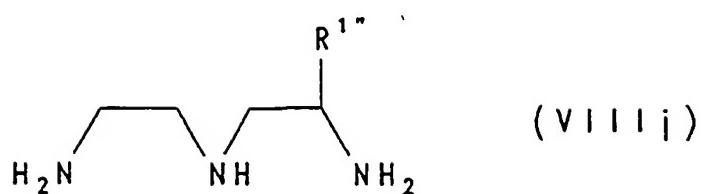


(VIII h)

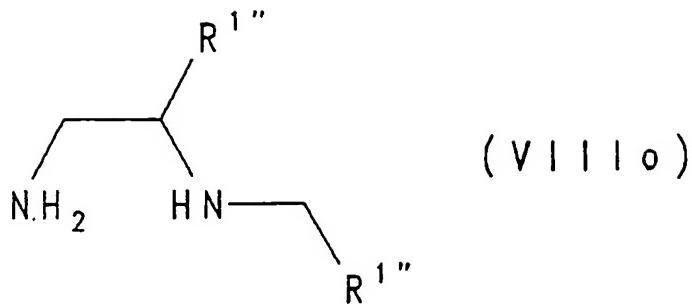


(VIII i)

12



13



(wherein each $R^{1''}$ is a protected R^1 group, e.g. a protected hydroxyalkyl group for example a $-CH_2-O-$ CH_2 -Phenyl group or a 2,2-dimethyl-1,3-dioxacyclopent-4-yl group). In these starting compounds, protected hydroxyalkyl groups attached to the alkylene chains between amine nitrogens are preferably benzyl protected groups and the nitrogen-attached protected hydroxyalkyl groups in $-CHR^1X''$ moieties are preferably in the form of cyclic polyethers.

The preparation of these starting compounds is as described in EP-A-299795 or may be carried out analogously.

Reaction of starting compounds of formulae VIII with sodium bromoacetate, and subsequent amidation and deprotection will yield corresponding compounds of formula I.

Amidation of the corresponding carboxyl compounds to produce the compounds of formula I can be performed in a conventional manner, e.g. as described by Salutar in US-A-4687659 or by Schering in EP-A-130934.

The amidation may conveniently be effected by reacting an acid anhydride of a compound of formula I (as defined above but excluding the proviso that at least one X group is of formula $CONR_2^2$) with an amine of formula IX

HNR_2^2 (IX)

(where each R^{2'} is an optionally protected R² group). Such reaction is preferably performed in the liquid phase. Thus for example a solution of the amine in a solvent such as water, dipolar aprotic solvents, such as acetonitrile, N-methylpyrrolidone, N-methylmorpholine, dimethylformamide, dimethylacetamide, dimethyl sulfoxide, tetrahydrofuran and the like or mixtures thereof is prepared. The anhydride is added in portions or optionally dissolved in a dipolar aprotic anhydrous solvent such as acetonitrile, N-methylpyrrolidone, N-methylmorpholine, dimethylformamide, dimethylacetamide, dimethyl sulfoxide, tetrahydrofuran and the like or mixtures thereof. The reaction mixture is stirred under a nitrogen atmosphere for a period ranging between 0.5 hour and 3 days, preferably between 1 hour and 24 hours. The reaction temperatures generally range between about 0°C and 100°C, temperatures of about 20°C to 80°C being preferred. For solvents with a low boiling point (100°C or less) the reaction mixture is evaporated to dryness and the product is isolated. For the solvents with higher boiling points a mixture of diethylether and chloroform may be added to precipitate the product.

Chelants of formula I may be used as the basis for bifunctional chelants or for polychelant compounds, that is compounds containing several independant chelant groups, by substituting for one X or R¹ group a bond or linkage to a macromolecule or polymer, e.g. a tissue specific biomolecule or a backbone polymer such as polylysine or polyethyleneimine which may carry several chelant groups and may itself be attached to a macromolecule to produce a bifunctional-polychelant. Such macromolecular derivatives of the compounds of formula I and the salts and metal chelates thereof form a further aspect of the present invention.

The linkage of a compound of formula I to a macromolecule or backbone polymer may be effected by any of the conventional methods such as the carbodiimide

method, the mixed anhydride procedure of Krejcarek et al. (see Biochemical and Biophysical Research Communications 77: 581 (1977)), the cyclic anhydride method of Hnatowich et al. (see Science 220: 613 (1983) and elsewhere), the backbone conjugation techniques of Meares et al. (see Anal. Biochem. 142: 68 (1984) and elsewhere) and Schering (see EP-A-331616 for example) and by the use of linker molecules as described for example by Nycomed in WO-A-89/06979.

Formation of salts and chelates of the chelants of the invention may again be performed in a conventional manner.

The chelating agents of the present invention are particularly suitable for use in detoxification or in the formation of metal chelates, chelates which may be used for example in or as contrast agents for in vivo or in vitro magnetic resonance (MR), X-ray or ultrasound diagnostics (e.g. MR imaging and MR spectroscopy), or scintigraphy or in or as therapeutic agents for radiotherapy, and such metal chelates form a particularly important embodiment of the present invention.

Salts or chelate complexes of the compounds of the invention containing heavy metal ions are particularly useful in diagnostic imaging or therapy. Especially preferred are salts or complexes with metals of atomic numbers 20-32, 42-44, 49 and 57 to 83, particularly Gd, Dy and Yb.

For use as an MR-diagnostics contrast agent, the chelated metal ion is particularly suitably a paramagnetic ion, the metal conveniently being a transition metal or a lanthanide, preferably having an atomic number of 21-29, 42, 44 or 57-71. Metal chelates in which the metal species is Eu, Gd, Dy, Ho, Cr, Mn or Fe are especially preferred and Gd³⁺, Mn²⁺ and Dy³⁺ are particularly preferred. For such use, the paramagnetic metal species is conveniently non-radioactive as

radioactivity is a characteristic which is neither required nor desirable for MR-diagnostics contrast agents. For use as X-ray or ultrasound contrast agents, the chelated metal species is preferably a heavy metal species, for example a non-radioactive metal with an atomic number greater than 37, preferably greater than 50, e.g. Dy³⁺. For use in scintigraphy and radiotherapy, the chelated metal species must of course be radioactive and any conventional complexable radioactive metal isotope, such as ^{99m}Tc or ¹¹¹In for example, may be used. For radiography, the chelating agent may be in the form of a metal chelate with for example ⁶⁷Cu, ¹⁵³Sm or ⁹⁰Y.

For use in detoxification of heavy metals, the chelating agent must be in salt form with a physiologically acceptable counterion, e.g. sodium, calcium, ammonium, zinc or meglumine, e.g. as the sodium salt of the chelate of the compound of formula I with zinc or calcium.

Where the metal chelate carries an overall charge, such as is the case with the prior art Gd DTPA, it will conveniently be used in the form of a salt with a physiologically acceptable counterion, for example an ammonium, substituted ammonium, alkali metal or alkaline earth metal cation or an anion deriving from an inorganic or organic acid. In this regard, meglumine salts are particularly preferred.

Viewed from a further aspect, the present invention provides a diagnostic or therapeutic agent comprising a metal chelate, whereof the chelating entity is the residue of a compound of formula I or salt thereof, together with at least one pharmaceutical or veterinary carrier or excipient, or adapted for formulation therewith or for inclusion in a pharmaceutical formulation for human or veterinary use.

Viewed from another aspect, the present invention provides a detoxification agent comprising a chelating

agent according to the invention in the form of salt with a physiologically acceptable counterion, together with at least one pharmaceutical or veterinary carrier or excipient, or adapted for formulation therewith or for inclusion in a pharmaceutical formulation for human or veterinary use.

The diagnostic and therapeutic agents of the present invention may be formulated with conventional pharmaceutical or veterinary formulation aids, for example stabilizers, antioxidants, osmolality adjusting agents, buffers, pH adjusting agents, etc. and may be in a form suitable for parenteral or enteral administration, for example injection or infusion or administration directly into a body cavity having an external escape duct, for example the gastrointestinal tract, the bladder or the uterus. Thus the agent of the present invention may be in a conventional pharmaceutical administration form such as a tablet, capsule, powder, solution, suspension, dispersion, syrup, suppository, etc; however, solutions, suspensions and dispersions in physiologically acceptable carrier media, for example water for injections, will generally be preferred.

The compounds according to the invention may therefore be formulated for administration using physiologically acceptable carriers or excipients in a manner fully within the skill of the art. For example, the compounds, optionally with the addition of pharmaceutically acceptable excipients, may be suspended or dissolved in an aqueous medium, with the resulting solution or suspension then being sterilized. Suitable additives include, for example, physiologically biocompatible buffers (as for example, tromethamine hydrochloride), additions (e.g., 0.01 to 10 mole percent) of chelants (such as, for example, DTPA, a DTPA-bisamide or non-complexed chelants of formula I) or calcium chelate complexes (as for example calcium DTPA,

CaNaDTPA-bisamide, calcium salts or chelates of chelants of formula I), or, optionally, additions (e.g., 1 to 50 mole percent) of calcium or sodium salts (for example, calcium chloride, calcium ascorbate, calcium gluconate or calcium lactate combined with metal chelate complexes of chelants formula I and the like).

If the compounds are to be formulated in suspension form, e.g., in water or physiological saline for oral administration, a small amount of soluble chelate may be mixed with one or more of the inactive ingredients traditionally present in oral solutions and/or surfactants and/or aromatics for flavouring.

For MRI and for X-ray imaging of some portions of the body the most preferred mode for administering metal chelates as contrast agents is parenteral, e.g., intravenous administration. Parenterally administrable forms, e.g., intravenous solutions, should be sterile and free from physiologically unacceptable agents, and should have low osmolality to minimize irritation of other adverse effects upon administration, and thus the contrast medium should preferably be isotonic or slightly hypertonic. Suitable vehicles include aqueous vehicles customarily used for administering parenteral solutions such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection and other solutions such as are described in Remington's Pharmaceutical Sciences, 15th ed., Easton: Mack Publishing Co., pp. 1405-1412 and 1461-1487 (1975) and The National Formulary XIV, 14th ed. Washington: American Pharmaceutical Association (1975). The solutions can contain preservatives, antimicrobial agents, buffers and antioxidants conventionally used for parenteral solutions, excipients and other additives which are compatible with the chelates and which will not interfere with the manufacture, storage or use of products.

Where the diagnostic or therapeutic agent comprises a chelate or salt of a toxic metal species, e.g. a heavy metal ion, it may be desirable to include within the formulation a slight excess of the chelating agent, e.g. as discussed by Schering in DE-A-3640708, or more preferably a slight excess of the calcium salt of such a chelating agent.

For MR-diagnostic examination, the diagnostic agent of the present invention, if in solution, suspension or dispersion form, will generally contain the metal chelate at concentration in the range 1 micromole to 1.5 mole per litre, preferably 0.1 to 700mM. The diagnostic agent may however be supplied in a more concentrated form for dilution prior to administration. The diagnostic agent of the invention may conveniently be administered in amounts of from 10^{-3} to 3 mmol of the metal species per kilogram of body weight, e.g. about 1 mmol Dy/kg bodyweight.

For X-ray examination, the dose of the contrast agent should generally be higher and for scintigraphic examination the dose should generally be lower than for MR examination. For radiotherapy and detoxification, conventional dosages may be used.

Viewed from a further aspect, the present invention provides a method of generating an image of the human or non-human animal body, which method comprises administering to said body a diagnostic agent according to the present invention and generating an X-ray, MR-diagnostics, ultrasound or scintigraphic image of at least a part thereof.

Viewed from a further aspect, the present invention provides a method of radiotherapy practised on the human or non-human animal body, which method comprises administering to said body a chelate of a radioactive metal species with a chelating agent according to the invention.

Viewed from a further aspect, the present invention provides a method of heavy metal detoxification

practised on the human or non-human animal body, which method comprises administering to said body a chelating agent according to the invention in the form of a salt with a physiologically acceptable counterion.

Viewed from a yet further aspect, the present invention also provides the use of the compounds, especially the metal chelates, according to the invention for the manufacture of diagnostic or therapeutic agents for use in methods of image generation, detoxification or radiotherapy practised on the human or non-human animal body.

Viewed from a still further aspect, the present invention provides a process for the preparation of the metal chelates of the invention which process comprises admixing in a solvent a chelant of formula I or a salt (e.g. the sodium salt) or chelate thereof together with an at least sparingly soluble compound of said metal, for example a chloride, oxide or carbonate.

Viewed from a yet still further aspect, the present invention provides a process for the preparation of the diagnostic or therapeutic agent of the present invention, which comprises admixing a metal chelate according to the invention, or a physiologically acceptable salt thereof, together with at least one pharmaceutical or veterinary carrier or excipient.

Viewed from a yet still further aspect, the present invention provides a process for the preparation of the detoxification agent of the invention, which comprises admixing a chelating agent according to the invention in the form of a salt with a physiologically acceptable counterion together with at least one pharmaceutical or veterinary carrier or excipient.

The disclosures of all of the documents mentioned herein are incorporated by reference.

The present invention will now be illustrated further by the following non-limiting Examples. All ratios and percentages given herein are by weight and all temperatures are in degrees Celsius unless otherwise

indicated.

EXAMPLE 1

3,9-Bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-6-carboxymethyl-4-(2-hydroxyethyl)-3,6,9-triazaundecane diacid

- a) 3,9-Bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-6-carboxymethyl-4-(2-acetyloxyethyl)-3,6,9-triazaundecane diacid

N-Methylaminopropanediol (0.20 g, 2.5 mmol) was dissolved in dry dimethylacetamide (DMA) (5 ml) and 1-(2-acetyloxyethyl)-1,5-bis(2,6-dioxomorpholino)-3-azapentane-3-acetic acid (0.5 g, 1.2 mmol) (prepared in accordance with EP-A-299795) was added. The mixture was stirred under nitrogen for 16 hours at ambient temperature. The title compound was precipitated with diethyl ether and chloroform to give a yellow oil. Yield 0.5 g (65%). FAB-MS: 654 (M+1). The structure was confirmed by ¹³C NMR.

- b) 3,9-Bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-6-carboxymethyl-4-(2-hydroxyethyl)-3,6,9-triazaundecane diacid

3,9-Bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-6-carboxymethyl-4-(2-acetyloxyethyl)-3,6,9-triazaundecane diacid (0.24 g, 0.37 mmol) was dissolved in methanol (20 ml) saturated with ammonia and stirred at ambient temperature overnight. The solvent was evaporated, and the residue was dissolved in water (10 ml) and washed with chloroform (2 x 10 ml). Evaporation yielded 0.2 g (89%). FAB-MS: 612 (M+1). The structure was confirmed by ¹³C NMR.

EXAMPLE 2

6-Carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid

- a) 4,8-Bis(benzyloxymethyl)-6-carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-3,6,9-triazaundecane diacid.

1,5-Bis(benzyloxymethyl)-1,5-bis(2,6-dioxomorpholino)-3-azapentane-3-acetic acid (44 g, 73 mmol) was dissolved in dry DMA (200 ml) and added to a solution of N-methylaminopropanediol (15 g, 146 mmol) in dry DMA (200 ml) on an ice bath. The mixture was stirred overnight at ambient temperature, and a solution of diethyl ether/chloroform (1/1) (200 ml) was added. The yellow oil was taken up in water (60 ml) and precipitated with acetone (4000 ml). The title product was isolated as a yellow solid. Yield: 47 g (80%). FAB-MS: 808 (M+1).

- b) 6-Carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid

4,8-Bis(benzyloxymethyl)-6-carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-3,6,9-triazaundecane diacid (40 g, 49 mmol) was dissolved in methanol (2000 ml) and ammonium formate (23 g, 363 mmol) was added. Palladium on carbon (10%) (64 g) was added under argon, and the suspension was stirred at 50°C for three hours. The catalyst was filtered off, and the title product was isolated by evaporation of the filtrate. Yield: 29 g (93%). FAB-MS: 628 (M+1).

Example 36-Carboxymethyl-3,9-bis(dimethylcarbamoylmethyl)-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid

- a) 4,8-Bis(benzyloxymethyl)-6-carboxymethyl-3,9-bis(dimethylcarbamoylmethyl)-3,6,9-triazaundecane diacid

1,5-Bis(benzyloxymethyl)-1,5-bis(2,6-dioxomorpholino)-3-azapentane-3-acetic acid (0.2 g, 0.34 mmol) was added to a solution of dimethylamine (40%) in water (10 ml) on an ice bath. The solution was stirred at ambient temperature overnight. The solvent was evaporated and the title product was isolated. Yield 0.23 g (98%).
FAB-MS: 688 (M+1).

- b) 6-Carboxymethyl-3,9-bis(dimethylcarbamoylmethyl)-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid

4,8-Bis(benzyloxymethyl)-6-carboxymethyl-3,9-bis(dimethylcarbamoylmethyl)-3,6,9-triazaundecane diacid (0.02 g, 0.04 mmol) was dissolved in methanol (15 ml) and ammonium formiate (0.02 g, 0.26 mmol) was added. Palladium on carbon (10 %) (0.045 g) was added under nitrogen, and the suspension was stirred at 50°C for three hours. The catalyst was filtered off and washed with methanol (5 ml). The filtrate was evaporated and the title product was isolated. Yield: 0.016 g (90%).
FAB-MS: 508 (M+1).

Example 46-Carboxymethyl-4,8-bis(hydroxymethyl)-3,9-bis(3-oxapentamethylenecarbamoylmethyl)-3,6,9-triazaundecane diacid

- a) 4,8-Bis(benzyloxymethyl)-6-carboxymethyl-3,9-bis(3-oxapentamethylencarbamoylmethyl)-3,6,9-triazaundecane diacid

1,5-Bis(benzyloxymethyl)-1,5-bis(2,6-dioxomorpholino)-3-azapentane-3-acetic acid (0.2 g, 0.34 mmol) was dissolved in DMA (2 ml) and morpholine (0.6 g, 0.68 mmol) was added, and the solution was stirred at ambient temperature overnight. The solvent was evaporated and the title product was isolated as a yellow oil. Yield: 0.2 g (77%). FAB-MS: 772 (M+1).

- b) 6-Carboxymethyl-4,8-bis(hydroxymethyl)-3,9-bis(3-oxapentamethylencarbamoylmethyl)-3,6,9-triazaundecane diacid

4,8-Bis(benzyloxymethyl)-6-carboxymethyl-3,9-bis(3-oxapentamethylencarbamoylmethyl)-3,6,9-triazaundecane diacid (0.18 g, 0.23 mmol) was dissolved in methanol (20 ml) and ammonium formiate (0.11 g, 1.7 mmol) was added. Palladium on carbon (10%) (0.3 g) was added under nitrogen, and the mixture was stirred at 50°C for three hours. The catalyst was filtered off and washed with methanol (5 ml). The filtrate was evaporated and the title product was isolated. Yield: 0.12 g (90%). FAB-MS: 592 (M+1).

Example 5

- 6-Carboxymethyl-4,8-bis(hydroxymethyl)-3,9-bis[N-methyl-(5-hydroxy-3-oxapentyl)carbamoylmethyl]-3,6,9-triazaundecane diacid

- a) 4,8-Bis(benzyloxymethyl)-6-carboxymethyl-3,9-bis[N-methyl-(5-hydroxy-3-oxapentylcarbamoylmethyl)]-3,6,9-triazaundecane diacid

1,5-Bis(benzyloxymethyl)-1,5-bis(2,6-dioxomorpholino)-3-

azapentane-3-acetic acid (0.2 g, 0.34 mmol) was dissolved in DMA (2 ml) and added to a solution of N-methyl-2-(2-hydroxyethoxy)ethylamine (0.08 g, 0.68 mmol) in DMA (0.5 ml). The solution was stirred overnight at ambient temperature, the solvent evaporated and the title product was isolated as a yellow oil. Yield: 0.12 g (44%). FAB-MS: 836 (M+1).

b) 6-Carboxymethyl-4,8-bis(hydroxymethyl)-3,9-bis[N-methyl-(5-hydroxy-3-oxapentylcarbamoylmethyl)]-3,6,9-triazaundecane diacid

1,5-Bis(benzylloxymethyl)-6-carboxymethyl-3,9-bis[N-methyl-(5-hydroxy-3-oxa-pentyl)-carbamoylmethyl)]-3,6,9-triazaundecane diacid (0.12 g, 0.14 mmol) was dissolved in methanol (20 ml) and ammonium formate (0.07 g, 1.6 mmol) was added. Palladium on carbon (10%) (0.19 g) was added under argon, and the suspension was stirred at 50°C for three hours. The catalyst was filtered off and washed with methanol. The filtrate was evaporated and the title product was isolated. Yield: 0.09 g (95%). FAB-MS: 656 (M+1).

Example 6

6-Carboxymethyl-4-(2-hydroxyethyl)-3,9-bis[N-methyl-(5-hydroxy-3-oxapentylcarbamoylmethyl)]-3,6,9-triazaundecane diacid

a) 4-(2-Acetoxyethyl)-6-carboxymethyl-3,9-bis[N-methyl-(5-hydroxy-3-oxapentylcarbamoylmethyl)]-3,6,9-triazaundecane diacid

1-(2-Acetoxyethyl)-1,5-bis-(2,6-dioxomorpholino)-3-azapentane-3-acetic acid (0.14 g, 0.34 mmol) is dissolved in DMA and added to a solution of N-methyl-2-(2-hydroxyethoxy)ethylamine (0.08 g, 0.68 mmol) in DMA. The solution is stirred overnight at ambient

temperature, the solvent is evaporated and the title product is isolated.

- b) 6-Carboxymethyl-4-(2-hydroxyethyl)-3,9-bis[N-methyl-(5-hydroxy-3-oxapentylcarbamoylmethyl)]-3,6,9-triazaundecane diacid

4-(2-Acetoxyethyl)-6-carboxymethyl-3,9-bis[N-methyl-(5-hydroxy-3-oxapentylcarbamoylmethyl)]-3,6,9-triazaundecane diacid is dissolved in methanol saturated with ammonia and stirred overnight at ambient temperature. The solvent is evaporated. The oil is taken up in water and washed with chloroform. The water is evaporated and the title product is isolated.

Example 7

6-Carboxymethyl-4,8-bis(hydroxymethyl)-3,9-bis-(3-hydroxypentamethylenecarbamoylmethyl)-3,6,9-triazaundecane diacid

- a) 4,8-Bis(benzyloxymethyl)-6-carboxymethyl-3,9-bis(3-hydroxypentamethylenecarbamoylmethyl)-3,6,9-triazaundecane diacid

1,5-Bis(benzyloxymethyl)-1,5-bis(2,6-dioxomorpholino)-3-azapentane-3-acetic acid (0.2 g, 0.34 mmol) is dissolved in DMA and added to a solution of 4-hydroxypiperidine (0.7 g, 0.68 mmol) in DMA. The solution is stirred overnight at ambient temperature, the solvent evaporated and the title product is isolated.

- b) 6-Carboxymethyl-4,8-bis(hydroxymethyl)-3,9-bis-(3-hydroxypentamethylenecarbamoylmethyl)-3,6,9-triazaundecane diacid

1,5-Bis(benzyloxymethyl)-6-carboxymethyl-3,9-bis(3-hydroxypentamethylenecarbamoylmethyl)-3,6,9-

triazaundecane diacid (0.11 g, 0.14 mmol) is dissolved in methanol and ammonium formate (0.07 g, 1.6 mmol) is added. Palladium on carbon (10%) (0.19 g) is added under argon, and the suspension is stirred at 50°C for three hours. The catalyst is filtered off and washed with methanol. The filtrate is evaporated and the title product is isolated.

Example 8

6-Carboxymethyl-4-(2-hydroxyethyl)-3,9-bis-(pentamethylenecarbamoylmethyl)-3,6,9-triazaundecane diacid

- a) 4-(2-Acetoxyethyl)-6-carboxymethyl-3,9-bis-(pentamethylenecarbamoylmethyl)-3,6,9-triazaundecane diacid

1-(2-Acetoxyethyl)-1,5-bis(2,6-dioxomorpholino)-3-azapentane-3-acetic acid (0.14 g, 0.34 mmol) is dissolved in DMA and added to a solution of piperidine (0.06 g, 0.68 mmol) in DMA. The solution is stirred overnight at ambient temperature, the solvent is evaporated and the title product is isolated.

- b) 6-Carboxymethyl-4-(2-hydroxyethyl)-3,9-bis-(pentamethylenecarbamoylmethyl)-3,6,9-triazaundecane diacid

4-(2-Acetoxyethyl)-6-carboxymethyl-3,9-bis-(pentamethylenecarbamoylmethyl)-3,6,9-triazaundecane diacid (0.10 g, 0.16 mmol) is dissolved in methanol saturated with ammonia and stirred overnight at ambient temperature. The solvent is evaporated. The oil is taken up in water and washed with chloroform. The water is evaporated and the title product is isolated.

Example 9Gadolinium(III) chelate of 3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-6-carboxymethyl-4-(2-hydroxyethyl)-3,6,9-triazaundecane diacid

The bis-amide from Example 1b (0.33 g, 0.54 mmol) was dissolved in water (10 ml), gadolinium(III) oxide (0.10 g, 0.27 mmol) was added and the mixture was refluxed overnight. The water was evaporated off and the title compound was isolated as a light yellow solid. Yield 0.4 g (96 %), FAB-MS: 767 (M+1).

Example 10Gadolinium(III) chelate of 6-carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid

6-Carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid (15.6 g, 24.8 mmol) (Example 2) was dissolved in water (250 ml) and gadolinium(III) chloride (8.83 g, 24.8 mmol) was added. The pH was adjusted to 6.4 with 5M NaOH (5 ml). The solution was stirred at ambient temperature for 15 minutes, filtered and the solvent was evaporated. The crude product was treated 3 times with methanol (3x30 ml) to remove inorganic salts. The suspension was filtered, the filtrate was evaporated and the title product was isolated. Yield: 18.4 g (95%). FAB-MS: 783 (M+1).

Example 11Dysprosium(III) chelate of 6-carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid

6-Carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid (0.15 g, 0.24 mmol) (Example 2) was dissolved in water (10 ml), dysprosium(III) oxide (0.45 g, 0.12 mmol) was added and the mixture was stirred at 80°C for 8 hours. The solution was filtered, the solvent evaporated and the title product was isolated. Yield: 0.19 g (99%). FAB-MS: 788 (M+1).

Example 12

Bismuth(III) chelate of 6-carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid

A neutral suspension of bismuth(III) hydroxide is prepared by neutralisation of a solution of bismuth(III) chloride (0.1 g, 0.52 mmol, 4 ml) with sodium hydroxide, followed by centrifugation of the precipitate and resuspension of the precipitate in water (4 ml). This solution is added to a neutral solution of 6-carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid (0.2 g, 0.32 mmol) (Example 2) in water (4 ml) and the mixture is refluxed for 4 hours. The clear solution is evaporated, and the title product is isolated.

Example 13

Preparation of a solution containing the gadolinium(III) chelate of 6-carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid

Gadolinium(III) chelate of 6-carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid (7.82 g, 10

mmol) (Example 10) was dissolved in 20 ml water. The solution was filtered, filled in a 20 ml vial and autoclaved. The solution contained 0.5 mmol gadolinium per ml.

Example 14

Preparation of a solution containing the trisodium salt of 6-carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid

6-Carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid (1.88 g, 3 mmol) (Example 2) was dissolved in water (15 ml), the pH was adjusted to 7 by careful addition of 1 M sodium hydroxide, water was added to 20 ml, the solution was filtered and filled into a 20 ml vial. The vial was autoclaved.

The solution contained 0.15 mmol of the trisodium salt of 6-carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid per ml.

The solution is for the treatment of acute or chronic poisoning by heavy metals such as lead.

Example 15

Vial containing the technetium chelate of 6-carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid

A vial is filled with 6-carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid (4 mg)

(Example 2) and tin(II) chloride (0.22 mg) as dry powder.

A solution of 99m Tc as pertechnetate in 0.9% sterile sodium chloride solution should be added before use. The technetium chelate with 6-carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid is for scintigraphic examination of organs such as the brain and kidneys. The chelate is also useful for study of kidney function.

Example 16

Preparation of a solution containing the sodium salt of the zinc(II) chelate of 6-carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid

6-Carboxymethyl-3,9-bis[N-methyl-(2,3-dihydroxypropylcarbamoylmethyl)]-4,8-bis(hydroxymethyl)-3,6,9-triazaundecane diacid (1.26 g, 2 mmol) (Example 2) and zinc(II) carbonate (0.25 g, 2 mmol) were refluxed for 12 hours in water (15 ml). The mixture was cooled to ambient temperature, the pH was adjusted to 6 by careful addition of 1M sodium hydroxide, water was added to 20 ml, the solution was filtered and filled into a 20 ml vial. The vial was autoclaved. The solution contained 0.1 mmol of the zinc chelate as its sodium salt per ml.

The solution is for the treatment of acute or chronic poisoning by heavy metals or radioactive metals such as plutonium.

Claims

1. Chelants of formula I



(wherein

A represents a group $>NCHR^1X$ or $>N(CHR^1)_pN(CHR^1X)_2$ or
 $A(CHR^1)_m$ represents a carbon nitrogen bond;
each X which may be the same or different represents a carboxyl group or a derivative thereof or a group R¹;
each R¹ which may be the same or different represents a hydrogen atom, a mono- or poly-hydroxyalkyl group or an alkoxy or alkoxyalkyl group optionally mono or polysubstituted by hydroxy and/or alkoxy groups; and n, m and p are each 2, 3 or 4, preferably 2; with the provisos that in at least two CHR¹X moieties X is a carboxyl group or a derivative thereof, that at least one group X of formula CONR²₂ where each R², which may be the same or different, represents an alkyl group optionally mono- or polysubstituted by hydroxy and/or alkoxy groups or NR²₂ represents a nitrogen-attached 5 to 7 membered saturated heterocyclic ring optionally containing a nitrogen, oxygen or sulphur atom as a further ring heteroatom and optionally substituted by one or more hydroxyl and/or R¹ groups and that at least one R¹ in a moiety (CHR¹X), (CHR¹)_m, (CHR¹)_n or (CHR¹)_p is other than hydrogen) and metal chelates and salts thereof.

2. Chelant as claimed in claim 1, wherein each CHR¹X group is other than a methyl group.

3. Chelant as claimed in either of claims 1 and 2, wherein no R¹ group in a CHR¹X moiety is a hydrophilic group and where no NR²₂ moiety is a heterocyclic ring, then at least one group X is of formula CONR²₂ where

each R² is an optionally mono- or polyhydroxylated alkyl group or a mono or polyhydroxylated alkoxy- or polyalkoxy- alkyl group.

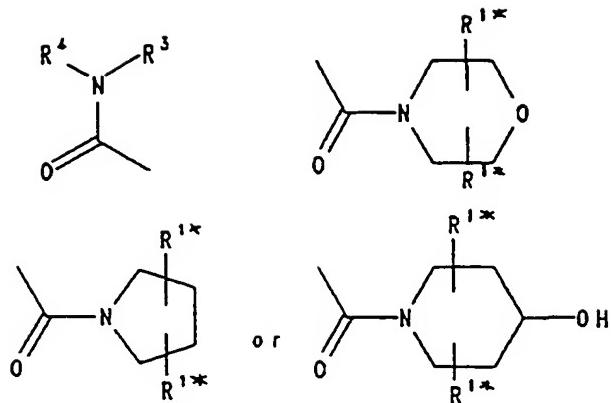
4. Chelant as claimed in either of claims 1 and 2, wherein no R¹ group in a (CHR¹)_n, (CHR¹)_p or (CHR¹)_q moiety is a hydrophilic group and where no NR²₂ moiety is a heterocyclic ring, then at least one group X is of formula CONR²₂ where each R² is an optionally mono- or polyhydroxylated alkyl group or a mono or polyhydroxylated alkoxy- or polyalkoxy- alkyl group.

5. Chelant as claimed in either of claims 3 and 4, wherein an R² group is hydroxy substituted at the terminal (omega) carbon.

6. Chelant as claimed in any of claims 1 to 5, wherein R¹ represents an alkoxy, polyalkoxy, hydroxyalkoxy, hydroxypolyalkoxy, polyhydroxyalkoxy, alkoxyalkyl, polyhydroxyalkyl, hydroxyalkoxyalkyl, hydroxypoly-alkoxyalkyl or polyhydroxypolyalkoxyalkyl group.

7. Chelant as claimed in any of claims 1 to 6, wherein at least one X group represents CONR¹¹₂ (where R¹¹ is a hydrogen atom or a group R² or NR¹¹₂ is a heterocyclic group as defined for NR²₂ in claim 1, COOR¹² (where R¹² is a hydrogen atom or an optionally hydroxylated, optionally alkoxylated alkyl group) and -COOM (wherein M⁺ is a monovalent cation or a fraction of a polyvalent cation).

8. Chelant as claimed in claim 7, wherein at least one X group is a formula



(where

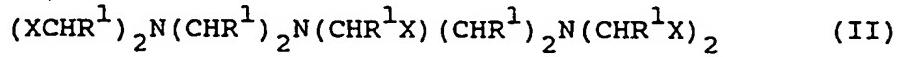
R^{1*} is an hydroxyl group or an R^1 group as defined in claim 1;

R^3 is an alkyl group; and

R^4 is an alkyl, hydroxyalkyl or hydroxyalkoxyalkyl group.

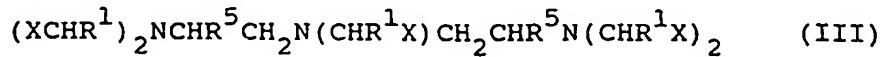
9. Chelant as claimed in any of claims 1 to 8, wherein each terminal amine nitrogen carries a group $CHR^1CONR_2^2$.

10. Chelant as claimed in any of claims 1 to 9, of formula II



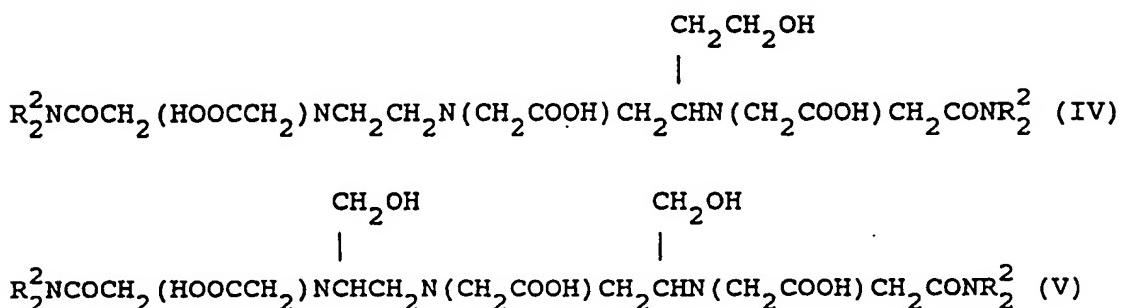
(where X and R^1 are as defined in claim 1) and the metal chelates and salts thereof.

11. Chelant as claimed in any of claims 1 to 10, of formula III



(where one R⁵ group is a hydroxy(C₁₋₄)alkyl group and the other R⁵ group is a hydrogen atom or a hydroxy(C₁₋₄)alkyl group and X and R¹ are as defined in claim 1) and the metal chelates and salts thereof.

12. Chelant as claimed in any of claims 1 to 11, of formula III or IV



(where NR₂² is as defined in claim 1) and the metal chelates and salts thereof.

13. A process for the preparation of compounds of formula I, said process comprising at least one of the following steps:

- i) reacting a corresponding amine to introduce a CHR¹X moiety at an amine nitrogen;
- ii) converting a carboxyl X moiety in a corresponding compound into a carboxyl derivative thereof or converting an carboxyl derivative X¹ moiety in a compound of formula I into a carboxyl group; and
- iii) converting a compound of formula I into a salt or metal chelate thereof or converting a salt or metal chelate of a compound of formula I into a compound of formula I.

14. A therapeutic agent comprising a metal chelate of a chelant as claimed in any of claims 1 to 12, or a salt thereof, together with at least one pharmaceutical or

veterinary carrier or excipient, or adapted for formulation therewith or for inclusion in a pharmaceutical formulation for human or veterinary use.

15. A diagnostic agent comprising a metal chelate of a chelant as claimed in any of claims 1 to 12, or a salt thereof, together with at least one pharmaceutical or veterinary carrier or excipient, or adapted for formulation therewith or for inclusion in a pharmaceutical formulation for human or veterinary use.

16. An agent as claimed in either of claims 14 and 15, wherein said chelate comprises a metal species with an atomic number of 20 to 32, 42 to 44, 49 or 57 to 83.

17. An agent as claimed in claim 16, wherein said metal species is Gd^{3+} , Mn^{2+} or Dy^{3+} .

18. A detoxification agent comprising a chelant as claimed in any of claims 1 to 12 in the form of salt with a physiologically acceptable counterion, together with at least one pharmaceutical or veterinary carrier or excipient, or adapted for formulation therewith or for inclusion in a pharmaceutical formulation for human or veterinary use.

19. A method of generating an image of the human or non-human animal body, which method comprises administering to said body a diagnostic agent as claimed in any of claims 15 to 17, and generating an X-ray, MR-diagnostics, ultrasound or scintigraphic image of at least a part thereof.

20. A method of radiotherapy practised on the human or non-human animal body, which method comprises administering to said body a chelate of a radioactive metal species with a chelant as claimed in any of claims

1 to 12.

21. A method of heavy metal detoxification practised on the human or non-human animal body, which method comprises administering to said body a chelant as claimed in any of claims 1 to 12 in the form of a salt with a physiologically acceptable counterion.

22. Use of a chelant as claimed in any of claims 1 to 12 for the manufacture of diagnostic or therapeutic agents for use in methods of image generation, detoxification or radiotherapy practised on the human or non-human animal body.

23. A process for the preparation of a metal chelate comprising admixing in a solvent a chelant as claimed in any of claims 1 to 12, or a salt or chelate thereof together with an at least sparingly soluble compound of said metal.

24. A process for the preparation of an agent as claimed in any of claims 14 to 17, comprising admixing a metal chelate as claimed in any of claims 1 to 12, or a physiologically acceptable salt thereof, together with at least one pharmaceutical or veterinary carrier or excipient.

25. A process for the preparation of a detoxification agent as claimed in claim 18 comprising admixing a chelant as claimed in any of claims 1 to 12, or a physiologically acceptable salt thereof, together with at least one pharmaceutical or veterinary carrier or excipient.

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